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Review Article

Evolution of Advanced Imaging Modalities in Multiple Myeloma

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Abstract

Multiple myeloma is a plasma cell neoplasm with frequent occurrence of osteolytic bone disease and associated complications. Novel diagnostic and therapeutic approaches in multiple myeloma have resulted in improved patient outcomes. While historically conventional skeletal survey was utilized to assess myeloma bone disease, significant limitations exist with this imaging modality. As a result, advanced imaging has emerged as a new standard and provides unique advantages and a more comprehensive evaluation both at diagnosis and throughout treatment course. Moving forward, combined or multi-modality imaging aims to augment our understanding of risk stratification and prognosis in multiple myeloma, thereby strengthening our management of patients with this complex disease.

Keywords: *Multiple Myeloma; Plasma Cell; Advanced Imaging; Lytic Bone Lesion; Myeloma Bone Disease*

Background

Multiple myeloma (MM) is an incurable and heterogenous neoplasm of clonal plasma cells that proliferate and produce abnormal monoclonal immunoglobulins [1]. Clinical manifestations of MM can include the development of hypercalcemia, renal insufficiency, anemia and/or lytic bone lesions (CRAB criteria), with bone disease occurring in up to 80% of patients with MM and serving as a major cause of morbidity [1,2]. The initiation of a diagnostic evaluation for MM can therefore be prompted by imaging that demonstrates concerning osseous lesions or by the discovery of monoclonal proteins. This plasma cell neoplasm falls on a disease spectrum with every case of MM believed to be anteceded by a precursor state referred to as monoclonal gammopathy of undetermined significance (MGUS) that may then progress to asymptomatic or smoldering multiple myeloma (SMM) and then finally to symptomatic or clinical multiple myeloma (CMM). The diagnosis of MM is based on identification of a monoclonal protein in the serum or urine of patients and abnormal clonal proliferation of plasma cells in the bone marrow and in the case of CMM necessitates evidence of end-organ injury that occurs due the effects of these malignant plasma cells. Updated diagnostic criteria for CMM from the International Myeloma Working Group (IMWG) now also incorporates patients with clonal plasmacytosis (bone marrow plasma cells > 10%) and one of three new biomarkers that have signaled high risk for development of more rapid progression to end-organ damage in clinical trials: clonal plasma cell burden > 60% in the bone marrow, serum free light chain ratio > 100, or more than one lytic bone lesion on magnetic resonance imaging (MRI) measuring > 5 mm in size [3]. Fortunately, the introduction of novel therapeutic agents has altered the landscape of MM and there has also been significant advancement in our approach to imaging in this complex patient population.

The disruption of bone and bone marrow architecture in MM arises due to the pathologic imbalance between osteoclastic and osteoblastic function, where osteoclasts become overactive and osteoblasts are unable to compensate for the increased bone breakdown [1,4]. This can potentially lead to the development of bone pain and fractures. Advanced imaging techniques have emerged as key components in the comprehensive evaluation of myeloma bone disease, both at diagnosis and in assessment of response to treatment, due to the widely recognized poor sensitivity of conventional skeletal survey (CSS). Imaging modalities including computed tomography (CT), MRI

and positron emission tomography (PET) are now routinely incorporated into the clinical management of patients with MM and most recent IMWG guidelines recommend utilization of whole-body low-dose CT (WB-LDCT) in place of CSS for the work-up of patients with newly diagnosed MM [5]. Furthermore, whole body MRI (WB-MRI) can improve the evaluation of bone marrow and soft tissue disruption from plasma cell neoplasm and can be used to assess the aggressiveness of myeloma bone lesions. Based on these advancements, current study in myeloma imaging is now focused on innovative combined or multi-modality techniques that may further augment our diagnostic and disease response assessment capabilities.

Conventional practices

Historically, CSS using plain radiographs was the primary imaging technique employed to detect myeloma bone lesions throughout the axial and appendicular skeleton [2,5]. CSS aims to identify lytic bone lesions, which are punched-out areas in the bone that lack reactive bone formation and indicate regions where bone marrow has been damaged and replaced with plasma cells [6-8]. Advantages of CSS include its low cost, widespread availability, and expansive skeletal coverage. However, imaging sensitivity is quite poor with CSS with studies showing that lytic bone lesions are often not detected on skeletal survey until 30-50% of the trabecular bone mass has been destroyed, prohibiting the identification of early or developing myeloma bone lesions which otherwise might influence treatment decisions [9]. In particular, visualization of lesions in the spine, pelvis, and rib cage are often suboptimal. The exact etiology of lytic bone changes on CSS may also be challenging to differentiate at time of detection and their appearance is generally not altered with anti-plasma cell treatment making response assessment impractical with CSS [10]. Due to its several shortcomings, CSS has fallen out of favor for use in MM and instead the field has moved towards utilization of advanced imaging modalities throughout the entirety of disease course.

Current practices

Use of advanced imaging in MM allows for a more robust determination of the nature of myelomatous bone and bone marrow involvement and provides valuable information regarding disease course. Osseous disease in MM can be quite heterogeneous and these imaging techniques allow for greater characterization of both bone and extramedullary (EM) disease. In 2019, the IMWG recommended that WB-LDCT be used in place of CSS as an initial component of the diagnostic work-up for CMM. Both PET-CT and axial or WB-MRI were also incorporated into routine imaging for myeloma bone disease, with WB-MRI recommended as a more sensitive imaging modality in patients who have a normal WB-LDCT and/or PET-CT [11]. WB-LDCT has been proposed for individuals with high risk MGUS, while the recommendation for optimal imaging of solitary plasmacytoma typically is use of WB-MRI or PET-CT imaging. Patients with suspected SMM should always undergo advanced imaging to rule out the presence of lytic bone lesions as a myeloma-defining event. PET-CT has also been incorporated into IMWG response assessment criteria, as the imaging component in the measurement of minimal residual disease (MRD) negativity for patients [11].

In contrast to CSS, WB-LDCT demonstrates improved sensitivity in detection of myeloma bone lesions with only 5% of trabecular bone destruction required to visualize these osseous abnormalities and it is performed with low dose or reduced radiation exposure [2,5,12]. Therefore, heightened sensitivity with CT allows for earlier identification of lytic bone lesions and can help guide therapeutic decision-making. WB-LDCT can also investigate for the presence and degree of involvement in surrounding soft tissues as well as provide an understanding of fracture risk and vertebral stability.

The benefit of PET-CT is that it combines anatomic and functional data to identify MM disease activity and to assess treatment response. PET imaging harnesses the movement of fluorodeoxyglucose (FDG) or ^{18}F into malignant plasma cells via glucose transporter 1 (GLUT1), where it becomes trapped and remains unmetabolized by cellular machinery [13,14]. This enables detection of isolated focal medullary lesions as well as disease outside of the bone marrow and in turn provides important knowledge on tissue pathophysiology and metabolism, a picture of overall tumor burden, rather than providing anatomic information alone as with CT and MRI. PET-CT has been shown to be more sensitive for focal osseous lesions when compared to CSS, however prior studies also suggested its inferiority when compared to

MRI spine and pelvis for identification of diffuse bone marrow involvement [15]. Studies with PET-CT have demonstrated prognostic implications both in regard to number of myeloma lesions at diagnosis and residual lesions at disease response assessment following initial anti-plasma cell therapy. It is important to note that concomitant infectious or inflammatory processes can confound findings on PET-CT and that skull lesions could be missed due to the increased physiologic FDG uptake typically seen in the brain [16].

MRI has been regarded as a gold standard for MM imaging and given its high sensitivity and excellent soft tissue contrast it is the modality of choice for bone marrow evaluation. In fact, IMWG guidelines dictate that if WB-LDCT is negative, a WB-MRI (or MRI of the spine and pelvis if WB-MRI is not available) should be performed as the next diagnostic step to exclude focal lytic bone lesions that may represent myeloma-defining events warranting initiation of therapy [17]. This imaging modality, therefore, has an important role in patients with SMM where the evaluation for more than one focal myeloma bone lesion is essential in differentiating SMM from CMM and establishing the most appropriate treatment plan. WB-MRI was demonstrated in a recent study of patients with SMM to be superior to spine MRI and PET-CT in identifying myelomatous involvement of the bone. This advanced imaging should be repeated on an annual basis in this patient population to ensure that no concerning osseous lesions develop over time [18,19]. Another benefit of WB-MRI over WB-LDCT or CSS is its high quality visualization of the spinal cord and nerve roots [9]. Disadvantages of WB-MRI include its high cost, longer imaging time, and use of gadolinium-based agents which could potentially lead to adverse reactions.

A unique feature of MRI imaging is the use of diffusion weighted MRI (DW-MRI), which works by detecting the different diffusion abilities of water in tissues. Studies have highlighted the ability of this functional imaging technique to distinguish patterns of diffuse bone marrow involvement in MM from normal bone marrow uptake [20]. DW-MRI has also been investigated as a part of disease response assessment in patients with MM who have undergone high dose chemotherapy and autologous stem cell rescue. The Myeloma Response Assessment and Diagnosis System (MY-RADS) recently formulated imaging recommendations with the aim to standardize response assessment in MM, including through use of a proposed Criteria for Response Assessment Category (RAC) scale which has not yet been extensively validated in clinical practice [21]. More recently, a retrospective analysis of 60 patients with MM who underwent DW-MRI at day 100 after high dose chemotherapy and autologous stem cell rescue illustrated the ability of DW-MRI to distinguish patients with different outcomes. However, concordance between DW-MRI and MRD by flow cytometry was low suggesting that these two tests should be combined to help enhance comprehensive response assessment and better define prognosis in MM patients who achieve a complete response by conventional response criteria [22]. Another study found significant correlation between plasma cell infiltration at the time of bone marrow biopsy and diffuse infiltration pattern detected by DW-MRI, suggesting that this functional imaging technique can be applied in assessment of residual osseous disease in patients with MM [23]. Finally, one study investigating the use of whole body STIR MRI with DWI in diagnosing lytic bone disease at an early, pre-symptomatic stage found that new focal myeloma bone lesions were detected in 50% of patients with slow biochemical relapse that otherwise may not have warranted a change in therapy. The authors of this study also noted that in the setting of the COVID-19 pandemic, this imaging modality could serve as a valuable tool in selecting a small group of patients with slow biochemical relapse who may be amendable to close observation rather than an immediate switch to salvage anti-plasma cell therapy [24].

Innovation in practice

Over the past several years, advancements in multi-modality imaging techniques have come to the forefront of myeloma imaging research and investigation. One such modality is FDG-PET/MRI, with this combination having the capability to provide simultaneous anatomic and metabolic data and overcome the weaknesses associated with its component imaging techniques when utilized independently [25]. When compared to PET-CT, FDG-PET/MRI serves as more sensitive technique for bone marrow infiltration by avoiding the risk of tracer uptake in the marrow that can obscure myeloma bone lesions on standard PET-CT, making this an attractive technique for both initial staging and disease response assessment in MM [26]. FDG-PET/MRI can provide information on extramedullary disease as well with the benefit of avoiding risks associated with irradiation. As our knowledge and experience continues to advance with this and other novel

imaging technology, we will be rewarded with a more refined approach to risk-stratification, response assessment, and overall prognosis in this complicated plasma cell neoplasm.

Yale-New Haven Hospital experience

The WB-MRI protocol at Yale-New Haven Hospital (YNHH) has served as a convenient and comprehensive radiologic modality for assessing osseous and soft tissue lesions in MM and has been utilized by practitioners beginning in 2015. The YNHH WB-MRI protocol utilizes a Siemens 3T scanner with moving table and an imaging time of 40 - 60 minutes to generate multi-planar, multi-sequence images [1) Sagittal T1 total spine, 2) Coronal STIR from skull vertex through ankles in 6 stations with merged images, 3) Coronal T1 from neck through feet in 5 stations with merged images]. In collaboration with our dedicated musculoskeletal radiology team, a YNHH WB-MRI Lesion Scoring System was created to help identify osseous lesions with higher risk features and better define the aggressiveness of myeloma bone lesions. This scoring system includes assessment of lesion size (< 1 cm, 1 - 3 cm, > 3 cm; 1 - 3 points), surrounding marrow or periosteal edema (1 point), cortical involvement (cortical breakthrough and/or endosteal scalloping; 1 point), and for the presence of associated soft tissue mass (1 point) with < 3 points total classified as less aggressive bone lesions and ≥ 3 points as more aggressive bone lesions. Investigation utilizing this innovative scoring system are ongoing at our institution [27].

Conclusion

The many diagnostic and therapeutic advances in MM over the last several decades have yielded improvement in survival and patient quality of life. However, this complex plasma cell neoplasm remains incurable and relapses are frequent and associated with significant morbidity. Due to the high probability of bone disease and associated complications, accurate and comprehensive imaging techniques are vital both at diagnosis and throughout disease course. Widespread study has confirmed the poor sensitivity of CSS and advanced imaging, which includes WB-LDCT, WB-MRI and PET-CT, has emerged to the forefront of clinical care in MM patients. These modalities each have distinct advantages and disadvantages, with WB-LDT providing information on early or developing myeloma bone lesions, WB-MRI allowing for high sensitivity detection of bone marrow involvement and potentially defining aggressiveness of myeloma bone lesions, and PET-CT combining anatomic and functional data for MM patients. Further innovation combining these advanced imaging techniques is underway and it is critical as we continue to advance our knowledge in imaging in MM that there be standardization to help guide enhanced risk stratification, prognostication and management for these patients.

Bibliography

1. Fairfield H., *et al*. "Multiple myeloma in the marrow: pathogenesis and treatments". *Annals of the New York Academy of Sciences 1364*.1 (2016): 32-51.

2. Amos B., *et al*. "Imaging of Multiple Myeloma". *Hematology/Oncology Clinics of North America* 30.4 (2016): 843-865.

3. Rajkumar SV., *et al*. "International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma". *The Lancet Oncology* 15.12 (2014): e538-548.

4. Rasch S., *et al*. "Multiple Myeloma Associated Bone Disease". *Cancers* 12.8 (2020).

5. Hillengass J., *et al*. "Whole-body computed tomography versus convential skeletal survey in patients with multiple myeloma: a study of the International Myeloma Working Group". *Blood Cancer Journal* 7.8 (2017): e599.

6. Dimopoulos M., *et al*. "International myeloma working group consensus statement and guidelines regarding the current role of imaging techniques in the diagnosis and monitoring of multiple myeloma". *Leukemia* 23.9 (2009): 1545-1556.

7. Heider U., *et al*. "Bone markers in multiple myeloma". *European Journal of Cancer* 42.11 (2006): 1544-1553.

8. Collins CD. "Multiple myeloma". *Cancer Imaging* 4 (2004): S47-53.

9. Derlin T and Bannas P. "Imaging of multiple myeloma: Current concepts". *World Journal of Orthopedics* 5.3 (2014): 272-282.

10. Wahlin A., *et al*. "Evaluation of serial bone X-ray examination in multiple myeloma". *Acta Medica Scandinavica* 212.6 (1982): 385-387.

11. Hillengass J., *et al*. "International myeloma working group consensus recommendations on imaging in monoclonal plasma cell disorders". *The Lancet Oncology* 20.6 (2019): e302-e312.

12. Hinge M., *et al*. "Baseline bone involvement in multiple myeloma - a prospective comparison of conventional X-ray, low-dose computed tomography, and 18flourodeoxyglucose positron emission tomography in previously untreated patients". *Haematologica* 101.10 (2016): e415-e418.

13. Tan E., *et al*. "Current and future imaging modalities for multiple myeloma and its precursor states". *Leukemia and Lymphoma* 52.9 (2011): 1630-1640.

14. Patching SG. "Roles of facilitative glucose transporter GLUT1 in [18F] FDG positron emission tomography (PET) imaging of human diseases". *Journal of Diagnostic Imaging in Therapy* 2.1 (2015): 30-102.

15. Zamagni E., *et al*. "A prospective comparison of 18F-fluorodeoxyglucose postitron emission tomography-computed tomography, magnetic responance imaging and while-body planar radiographsi in the assessment of bone disease in newly adignosed multiple myeloma". *Haematologica* 92.1 (2007): 50-55.

16. Caers J., *et al*. "The role of positron emission tomography-computed tomography and magnetic responance imaging in diagnosis and follow-up of multiple myeloma". *Haematologica* 99.4 (2014): 629-637.

17. Mulé S., *et al*. "Whole-Body Functional MRI and PET/MRI in Multiple Myeloma". *Cancers* 12.11 (2020): 3155.

18. Hill E., *et al*. "Evaluation of Whole-Body MRI (WB-MRI) in Smoldering Multiple Myeloma (SMM)". *Blood* 136.1 (2020): 19-20.

19. Wennmann M., *et al*. "Spatial Distribution of Focal Lesions in Whole-Body MRI and Influence of MRI Protocol on Staging in Patients with Smoldering Multiple Myeloma According to the New SLiM-CRAB-Criteria". *Cancers* 12.9 (2020): 2537.

20. Terpos E., *et al*. "Diffuse-Weighted Magnetic Resonance Imaging (DW-MWI) Is Able to Distinguish Diffuse from Normal MRI Pattern of Marrow Involvement in Patients with Multiple Myeloma". *Blood* 124.21 (2014): 3461-3461.

21. Messiou C., *et al*. "Guidelines for Acquisition, Interpretation, and Reporting of Whole-Body MRI in Myeloma: Myeloma Response Assessment and Diagnosis System (MY-RADS)". *Radiology* 291.1 (2019): 5-13.

22. Belotti A., *et al*. "External Validation of Diffusion Weighted Whole Body MRI (DW-MRI) Response Assessment Category (RAC) Criteria Proposed By the Myeloma Response Assessment and Diagnosis System (MY-RADS) Imaging Recommendations: Prognostic Role of Imaging Response after Transplant in Multiple Myeloma and Comparison with MRD Evaluation By Flow Cytometry". *Blood* 136.1 (2020): 41-42.

23. Mangiacavalli S., *et al*. "Whole Body Diffusion Weighted MRI (WB DWI) for the Management of Multiple Myeloma: High Concordance between MRI Diffuse Pattern and BONE Marrow Plasma CELL Infiltration RATE". *Blood* 134.1 (2019): 5495-5495.

24. Rowland J and Mollee P. "The Role of Whole Body STIR MRI in Assessing First Biochemical Relapse in Patients with Myeloma". *Blood* 136.1 (2020): 55-55.

25. Garderet L., *et al*. "The Role of PET-MRI in Multiple Myeloma Patients". *Blood* 136.1 (2020): 12-12.

26. Fraum TJ., *et al*. "Imaging of Plasma Cell Dyscrasias with FDG-PET/MRI: A Single-Center Experience". *Blood* 128.22 (2016): 5611-5611.

27. Browning S., *et al*. "Outcomes of Whole Body Magnetic Resonance Imaging for Evaluation of Multiple Myeloma Lesions, A New Scoring System in Practice". *American Journal of Hematology* 95(20200): S4.

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